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Manipulation of immunometabolism by HIV — accessories to the crime?

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Evolutionary pressure has produced an 'arms race' between cellular restriction factors (limiting viral replication) and viral proteins (overcoming host restriction). The host factors SAMHD1 and SLFN1 patrol metabolic bottlenecks required for HIV replication. Conversely, the HIV accessory proteins Vpx, Vpu and Nef manipulate cellular metabolism to enable viral replication. Recent work identifying Vpu-mediated downregulation of the alanine transporter SNAT1 and Nef-mediated downregulation of the serine carriers SERINC3/5 has uncovered the importance of HIV manipulation of the amino acid supply. Interference with CD4+ T-cell amino acid metabolism suggests a novel paradigm of viral immunomodulation, and signposts fundamental aspects of lymphocyte biology.

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Introduction

Human Immunodeficiency Virus (HIV) infects almost 40 million people worldwide and causes more than 1 million AIDS-related deaths every year (latest data available from www.unaids.org). In addition to the Gag, Pol and Env polyproteins common to all retroviruses, HIV encodes the so-called 'accessory proteins' Vif, Vpr, Nef and Vpu/Vpx, dispensable for viral replication *in vitro*, but essential for viral pathogenesis *in vivo* (Figure 1; reviewed in [1]). Vif, Vpr and Nef are common to all strains of HIV, but Vpu is found only in HIV-1 (responsible for the global AIDS pandemic), and Vpx is found only in HIV-2 (responsible for a minority of infections, particularly in West Africa). As well as counteracting host-cell restriction and promoting immune evasion (reviewed in [2]), recent results suggest that HIV accessory proteins directly manipulate cellular metabolic pathways to optimise the intracellular environment for productive infection (Figure 2). They are therefore accomplices, rather than accessories to the crime.

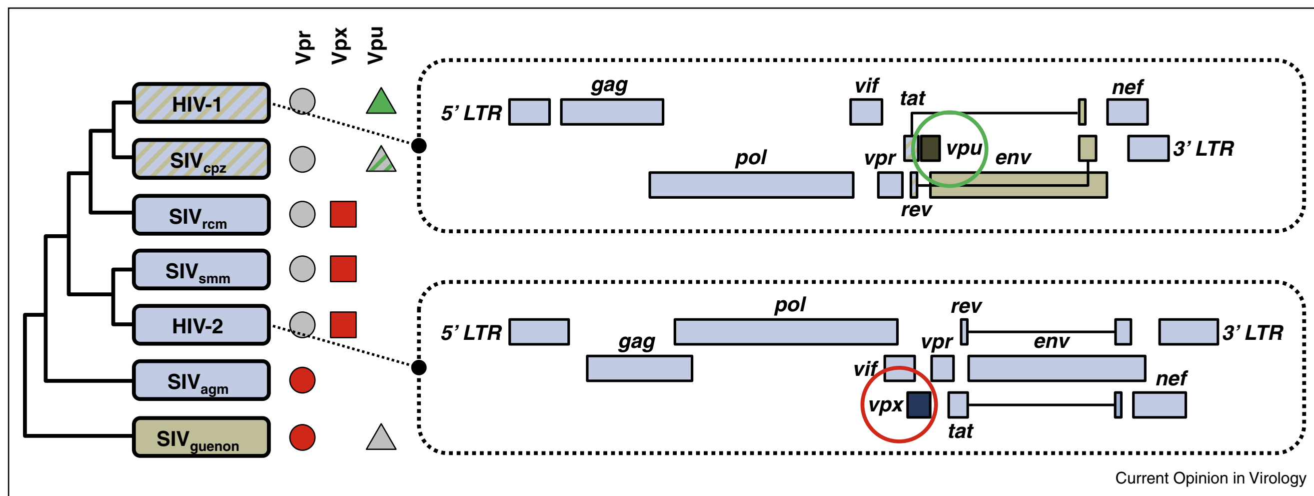
Whilst all viruses co-opt cellular metabolism to enable their replication, two characteristics of HIV infection *in vivo* present specific challenges. First, like all retroviruses, HIV relies on reverse transcription for replication of its genome. Second, the HIV entry receptor CD4 is expressed by both resting (naïve) and activated helper T-cells, as well as terminally differentiated macrophages, a range of cells with markedly different metabolic programmes. In this review, we describe how HIV accessory proteins enable the virus to overcome these challenges by manipulating the metabolism of nucleotides, glucose, amino acids and lipids. We discuss cellular restriction factors which patrol metabolic pathways required for viral replication, and focus on recent discoveries highlighting HIV-mediated remodelling of the plasma membrane and interference with the T-cell nutrient supply.

Expansion of the nucleotide pool

Like all retroviruses, HIV encodes reverse transcriptase to generate complementary ssDNA from its positive-sense ssRNA genome, utilising cellular deoxynucleotide triphosphates (dNTPs) as substrates for DNA polymerisation. This metabolic bottleneck is exploited therapeutically by nucleoside/nucleotide and non-nucleoside reverse transcriptase inhibitors, which have formed the backbone of anti-retroviral drug therapy since zidovudine (AZT) was approved for the treatment of HIV in 1987. Productive HIV-1 infection in resting primary CD4+ T-cells and myeloid cells is inhibited at the level of reverse transcription by the scarcity of intracellular dNTPs (reviewed in [3]). Low concentrations of dNTPs are maintained by the recently described deoxynucleotide phosphohydrolase SAMHD1, which hydrolyses dNTPs to deoxynucleosides and free triphosphates, and therefore acts as a metabolic restriction factor [4••,5••]. Conversely, an expanded dNTP pool is characteristic of activated T-cells and transformed/cancerous cell lines, enabling cellular DNA replication and relieving the block to reverse transcription [3].

Vpx of HIV-2 targets SAMHD1 for ubiquitin-dependent proteasomal degradation and, when incorporated into virions, overcomes the block to HIV reverse transcription in resting T-cells and myeloid cells [4••,6,7]. Vpx is paralogous to Vpr, and Vpr variants of most primate

Figure 1



Evolutionary origins of the HIV accessory proteins. Indicative phylogenetic relationships of selected primate lentiviruses (left panel) and genomic structures of HIV-1 and HIV-2 (right panels) are shown. Viruses encoding Vpr (circles), Vpx (squares) and Vpu (triangles) are indicated, and variants able to antagonise SAMHD1 (Vpr or Vpx; red) and SNAT1 (Vpu; green) are highlighted. Almost all HIV infections are caused by HIV-1 group M viruses, which arose from chimpanzee SIV_{cpz} by cross-species transmission in the Congo river basin in the early 1900s [60]. SIV_{cpz} was itself derived from recombination between red capped mangabey SIV_{rcm} and an ancestral Vpu-containing SIV related to the modern guenon monkey SIV_{gsn}, SIV_{mus} and SIV_{mon} viruses (SIV_{guenon}; reviewed in [61]). This recombination endowed SIV_{cpz}/HIV-1 viruses with Vpu, but restructuring of the C-terminus of Vif to allow antagonism of human APOBEC3G resulted in loss of Vpx [9]. Downregulation of SNAT1 is restricted to Vpu variants of HIV-1 group M viruses and some SIV_{cpz}/HIV-1 group N viruses [23••]. A minority of HIV infections are caused by HIV-2 viruses, which arose from sooty mangabey monkey SIV_{smm} by multiple cross-species transmissions in West Africa, and therefore encode Vpx but not Vpu [61]. Regions of HIV-1/2 derived from mangabey $SIV_{rcm/smm}$ (blue) and guenon monkey SIV_{guenon} (tan) viruses are highlighted. All primate lentiviruses encode Vif and Nef, and Vif is also found in other non-primate lentiviral lineages. Adapted from published phylogenetic trees [8,9,23••,61] and genomic maps for HIV-1 HXB2 and HIV-2 BEN available from www.hiv.lanl.gov. LTR, long terminal repeat.

lentiviruses lacking Vpx demonstrate species-specific antagonism of SAMHD1 [8]. This activity was surrendered by the cross-species transmission and recombination event that generated SIV_{cpz}, and has not been reacquired by viruses of the SIV_{cpz}/HIV-1 lineage [9]. The absence of SAMHD1 antagonism in HIV-1 may have been partially compensated by the enhanced affinity (low Km) of HIV-1 reverse transcriptase for dNTPs [10], but it is also possible that the avoidance of productive replication in professional antigen presenting cells is itself an adaptive strategy for immune evasion.

Induction of glycolysis

As well as increasing dNTP availability, T-cell activation results in profound upregulation of glucose uptake and glycolytic flux, a process similar to oncogenic transformation (reviewed in [11,12]). As with cancer cells, aerobic glycolysis provides ATP, NADPH and the molecular building blocks for cellular biomass [13], and glycolysis is required to support the replication of a range of viruses (reviewed in [14,15]). Similarly, HIV infection of primary T-cells enhances glucose uptake and glycolytic flux [16•,17], and the cell surface glucose transporter GLUT1 is required for both T-cell activation and efficient HIV replication [18,19]. The mechanism by which HIV enhances glycolysis has not been elucidated. However, it appears to be specific for primary T-cells, because enhanced glycolysis was not observed in HIV-infected Jurkat or CEM-SS (T-cell) or U937/U1 (monocyte/macrophage) models [16•,17], and unlike T-cell activation, does not reflect increased expression of GLUT1 at the plasma membrane [17].

Cutting the amino acid supply

Whilst facilitating HIV replication, T-cell activation also triggers activation-induced cell death (AICD), limiting the life-span of infected cells [20]. Likewise, whilst glucose starvation inhibits virus production, it also prolongs survival of infected cells [17]. HIV-1 replication *in vivo* is therefore likely to be favoured by intermediate levels of T-cell activation [21], and Nef modulates signalling from the T-cell receptor (TCR) at several levels [22]. Attention has focussed on downregulation of the TCR-CD3 T-cell receptor complex by Nef variants of non-pathogenic SIVs, which may limit immune activation by reducing AICD and inflammatory cytokine release from infected cells [20]. Conversely, the ability to downregulate TCR-CD3 is attenuated in Nef variants of HIV-1 and most Vpu-containing primate lentiviruses [20], We recently used Tandem Mass Tag (TMT)-based plasma membrane proteomics to gain a comprehensive, unbiased overview of global changes in the cell surface landscape of

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